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APPLICATION

FOR

UNITED STATES LETTERS PATENT

APPLICANTS: Alexis Borisy, Curtis Keith, Michael A. Foley, Brent R. Stockwell, Debra A. Gaw, M. James Nichols, and Margaret S. Lee,

TITLE: COMBINATIONS OF DRUGS FOR THE TREATMENT OF NEOPLASMS

COMBINATIONS OF DRUGS FOR THE TREATMENT OF NEOPLASMS

Cross-Reference to Related Applications

This application claims benefit from U.S. Application No. 60/395,233, filed July 11, 2002, which is hereby incorporated by reference.

Background of the Invention

The present invention relates to the treatment of neoplasms such as cancer.

Cancer is a disease marked by the uncontrolled growth of abnormal cells. Cancer cells have overcome the barriers imposed in normal cells, which have a finite lifespan, to grow indefinitely. As the growth of cancer cells continue, genetic alterations may persist until the cancerous cell has manifested itself to pursue a more aggressive growth phenotype. If left untreated, metastasis, the spread of cancer cells to distant areas of the body by way of the lymph system or bloodstream, may ensue, destroying healthy tissue.

The treatment of cancer has been hampered by the fact that there is considerable heterogeneity even within one type of cancer. Some cancers, for example, have the ability to invade tissues and display an aggressive course of growth characterized by metastases. These tumors generally are associated with a poor outcome for the patient. Ultimately, tumor heterogeneity results in the phenomenon of multiple drug resistance, i.e., resistance to a wide range of structurally unrelated cytotoxic anticancer compounds, J. H. Gerlach et al., *Cancer Surveys*, 5:25-46 (1986). The underlying cause of progressive drug resistance may be due to a small population of drug-resistant cells within the tumor (e.g., mutant cells) at the time of diagnosis, as described, for example, by J. H. Goldie and Andrew J. Coldman, *Cancer Research*, 44:3643-3653 (1984). Treating such a

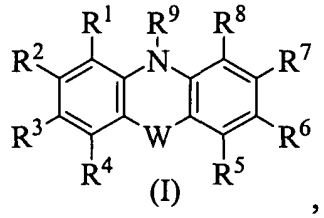
tumor with a single drug can result in remission, where the tumor shrinks in size as a result of the killing of the predominant drug-sensitive cells. However, with the drug-sensitive cells gone, the remaining drug-resistant cells can continue to multiply and eventually dominate the cell population of the tumor. Therefore, the problems of why metastatic cancers develop pleiotropic resistance to all available therapies, and how this might be countered, are the most pressing in cancer chemotherapy.

Anticancer therapeutic approaches are needed that are reliable for a wide variety of tumor types, and particularly suitable for invasive tumors. Importantly, the treatment must be effective with minimal host toxicity. In spite of the long history of using multiple drug combinations for the treatment of cancer and, in particular, the treatment of multiple drug resistant cancer, positive results obtained using combination therapy are still frequently unpredictable.

Summary of the Invention

The present invention features a combination therapy involving the use of pentamidine, or an analog of pentamidine, and chlorpromazine, or an analog of chlorpromazine. A combination of these two agents has been found to be beneficial in the treatment of neoplasms.

Accordingly, in a first aspect, the invention features a method for treating a patient having a neoplasm, by administering to the patient a first compound having the formula (I):

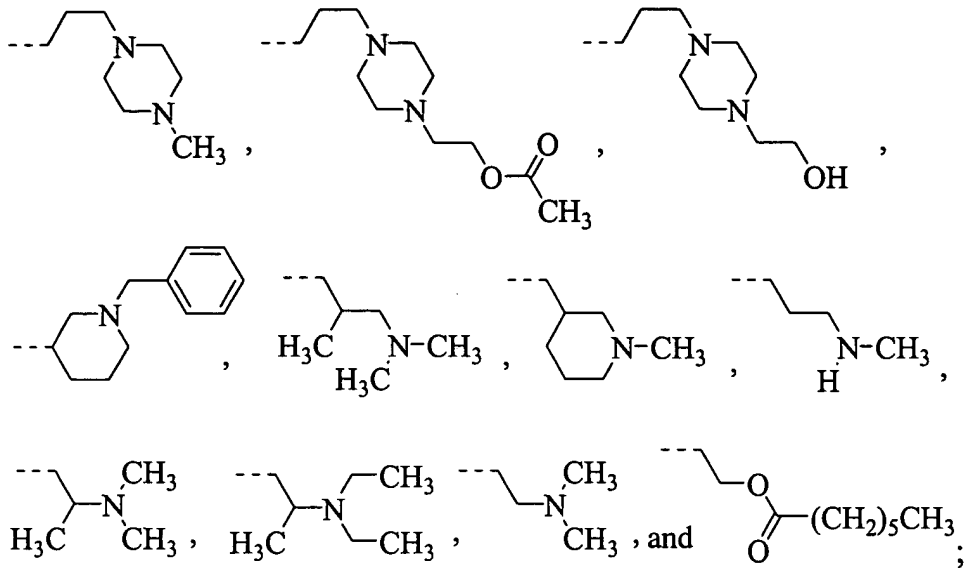


(I) ,

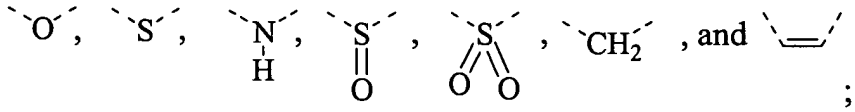
or a pharmaceutically acceptable salt thereof,

wherein R^2 is selected from the group consisting of: CF_3, halo, OCH_3, $COCH_3$, CN, OCF_3, $COCH_2CH_3$, $CO(CH_2)_2CH_3$, and SCH_2CH_3;

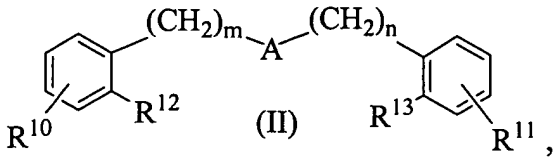
R^9 is selected from the group consisting of:



each of R^1, R^3, R^4, R^5, R^6, R^7, and R^8 is independently H, OH, F, OCF_3, or OCH_3; and W is selected from the group consisting of:

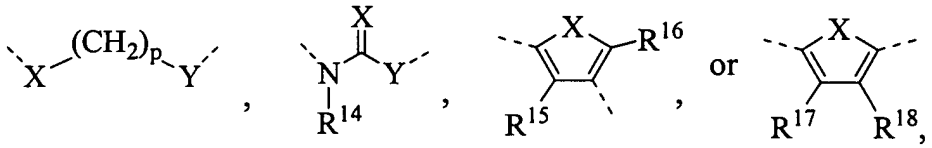


and, b) a second compound of formula (II):



or a pharmaceutically acceptable salt thereof,

wherein A is



wherein

each of X and Y is, independently, O, NR^{19}, or S,

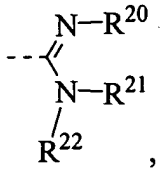
each of R^{14} and R^{19} is, independently, H or C_1-C_6 alkyl,

each of R^{15}, R^{16}, R^{17}, and R^{18} is, independently, H, C_1-C_6 alkyl, halogen, C_1-C_6 alkyloxy,C_6-C_{18} aryloxy, or C_6-C_{18} aryl-C_1-C_6 alkyloxy,

p is an integer between 2 and 6, inclusive,

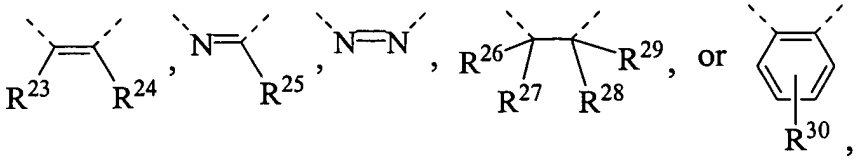
each of m and n is, independently, an integer between 0 and 2, inclusive,

each of R^{10} and R^{11} is



,

wherein R^{21} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy-C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, carbo(C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryl C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



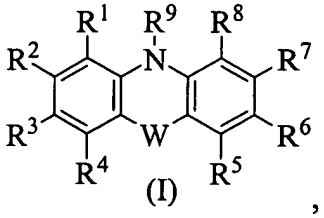
wherein each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, R^{28}, and R^{29} is, independently, H or C_1-C_6 alkyl, and R^{30} is H, halogen, trifluoromethyl, OCF_3, NO_2, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl,

each of R^{12} and R^{13} is, independently, H, Cl, Br, OH, OCH_3, OCF_3, NO_2, and NH_2, or R^{12} and R^{13} together form a single bond.

The invention also features compositions that include a compound of formula (I) and a compound of formula (II) and a pharmaceutically acceptable carrier.

Preferably, the compound of formula (I) is acepromazine, chlorfenethazine, cyamemazine, enanthate, fluphenazine, mepazine, methotrimeprazine, methoxypromazine, norchlorpromazine, perazine, perphenazine, prochlorperazine, promethazine, propiomazine, putaperazine, thiethylperazine, thiopropazate, thioridazine, trifluoperazine, or triflupromazine and the compound of formula (II) is pentamidine, propamidine, butamidine, heptamidine, nonamidine, stilbamidine, hydroxystilbamidine, diminazene, dibrompropamidine, 2,5-bis(4-amidinophenyl)furan, 2,5-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,5-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,5-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,4-bis(4-amidinophenyl)furan, 2,4-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,4-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,5-bis(4-amidinophenyl) thiophene, 2,5-bis(4-amidinophenyl) thiophene-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)thiophene, 2,4-bis(4-amidinophenyl)thiophene-bis-O-methylamidoxime. Most preferably, the compound of formula (I) is chlorpromazine, perphenazine or promethazine and the compound of formula (II) is pentamidine, 2,5-bis(4-amidinophenyl)furan, or 2,5-bis(4-amidinophenyl)furan-bis-O-methylamidoxime.

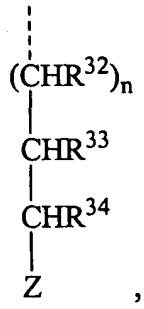
In a related aspect, the invention features another method for treating a patient having a neoplasm, by administering to the patient a first compound having the formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

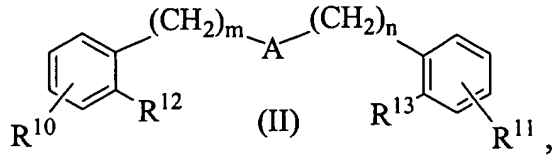
wherein R^9 has the formula:



,

wherein n is 0 or 1, each of R^{32}, R^{33}, and R^{34} is, independently, H or substituted or unsubstituted C_{1-6} alkyl, and Z is $NR^{35}R^{36}$ or OR^{37}, wherein each of R^{35} and R^{36} is, independently, H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkaryl, substituted or unsubstituted alkheteroaryl, and R^{37} is H, C_{1-6} alkyl, or C_{1-7} acyl, wherein any of R^{33}, R^{34}, R^{35}, and R^{36} can be optionally taken together with intervening carbon or non-vicinal O, S, or N atoms to form one or more five- to seven-membered rings, substituted with one or more hydrogens, substituted or unsubstituted C_{1-6} alkyl groups, C_{6-12} aryl groups, alkoxy groups, halogen groups, substituted or unsubstituted alkaryl groups, or substituted or unsubstituted alkheteroaryl groups;

and, b) a second compound having the formula (II):

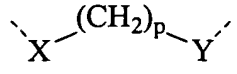


(II)

,

or a pharmaceutically acceptable salt thereof,

wherein A is



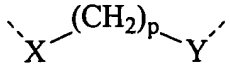
,

each of X and Y is independently O or NH;

p is an integer between 2 and 6, inclusive; and

m and n are, independently, integers between 0 and 2, inclusive, wherein the sum of m and n is greater than 0;

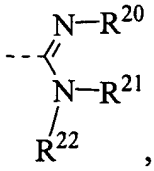
or A is



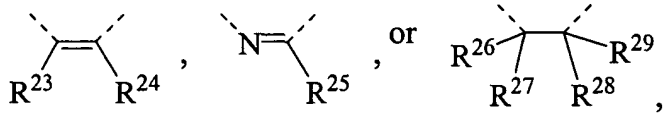
each of X and Y is independently O or NH,

each of m and n is 0, and

each of R^{10} and R^{11} is, independently, selected from the group represented by

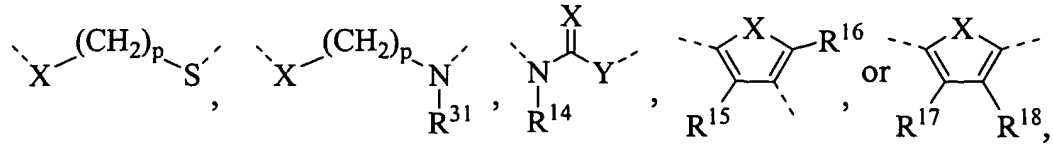


wherein R^{21} is C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, carbo(C_1-C_6 alkoxy), carbo(C_6-C_{18} aryl C_1-C_6 alkoxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



wherein each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, and R^{28} is, independently, H or C_1-C_6 alkyl, and R^{29} is C_1-C_6 alkyl, C_1-C_6 alkyloxy, or trifluoromethyl;

or A is



each of X and Y is, independently, O, NR^{19}, or S,

each of R^{14} and R^{19} is, independently, H or C_1-C_6 alkyl,

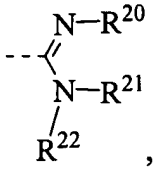
each of R^{15}, R^{16}, R^{17}, and R^{18} is, independently, H, C_1-C_6 alkyl, halogen, C_1-C_6 alkyloxy, C_6-C_{18} aryloxy, or C_6-C_{18} aryl C_1-C_6 alkyloxy,

R^{31} is C_1-C_6 alkyl,

p is an integer between 2 and 6, inclusive,

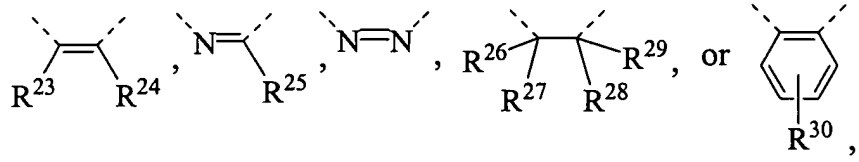
each of m and n is, independently, an integer between 0 and 2, inclusive,

each of R^{10} and R^{11} is, independently, selected from the group represented by



,

wherein R^{21} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, carbo(C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryl C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



wherein each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, R^{28}, and R^{29} are, independently, H or C_1-C_6 alkyl, and R^{30} is H, halogen, trifluoromethyl, OCF_3, NO_2, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl.

Preferably, the compound of formula (I) is acepromazine, chlorfenethazine, chlorpromazine, cyamemazine, enanthate, fluphenazine, mepazine,

methotrimeprazine, methoxypromazine, norchlorpromazine, perazine, perphenazine, prochlorperazine, promethazine, propiomazine, putaperazine, thiethylperazine, thiopropazate, thioridazine, trifluoperazine, or triflupromazine and the compound of formula (II) is propamidine, butamidine, heptamidine, nonamidine, stilbamidine, hydroxystilbamidine, diminazene, dibrompropamidine, 2,5-bis(4-amidinophenyl)furan, 2,5-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,5-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,5-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,4-bis(4-amidinophenyl)furan, 2,4-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,4-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,5-bis(4-amidinophenyl) thiophene, 2,5-bis(4-amidinophenyl) thiophene-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)thiophene, 2,4-bis(4-amidinophenyl)thiophene-bis-O-methylamidoxime. Most preferably, the compound of formula (I) is chlorpromazine, perphenazine or promethazine and the compound of formula (II) is pentamidine, 2,5-bis(4-amidinophenyl)furan, or 2,5-bis(4-amidinophenyl)furan-bis-O-methylamidoxime.

The first and second compounds are administered within 14 days of each other, in amounts sufficient to inhibit the growth of the neoplasm. Preferably, the two compounds are administered within ten days of each other, more preferably within five days of each other, and most preferably within twenty-four hours of each other or even simultaneously.

In another aspect, the invention features a method for treating a patient having a neoplasm such as cancer. In this method the patient is administered, (a) a first compound selected from prochlorperazine, perphenazine, mepazine, methotrimeprazine, acepromazine, thiopropazate, perazine, propiomazine, putaperazine, thiethylperazine, methopromazine, chlorfenethazine, cyamemazine, perphenazine, norchlorpromazine, trifluoperazine, thioridazine (or a salt of any of the above), and dopamine D2 antagonists (e.g., sulpride, pimozide, spiperone,

ethopropazine, clebopride, bupropion, and haloperidol), and, (b) a second compound selected from pentamidine, propamidine, butamidine, heptamidine, nonamidine, stilbamidine, hydroxystilbamidine, diminazene, benzamidine, phenamidine, dibrompropamidine, 1,3-bis(4-amidino-2-methoxyphenoxy)propane, phenamidine, amicarbalide, 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,3-bis(4'-(N-hydroxyamidino)phenoxy)propane, 1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane, 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane, 1,3-bis(4'-(4-hydroxyamidino)phenoxy)propane, 1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 2,5-bis[4-amidinophenyl]furan, 2,5-bis[4-amidinophenyl]furan-bis-amidoxime, 2,5-bis[4-amidinophenyl]furan-bis-O-methylamidoxime, 2,5-bis[4-amidinophenyl]furan-bis-O-ethylamidoxime, 2,5-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,5-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,4-bis(4-amidinophenyl)furan, 2,4-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,4-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,5-bis(4-amidinophenyl) thiophene, 2,5-bis(4-amidinophenyl) thiophene-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)thiophene, 2,4-bis(4-amidinophenyl)thiophene-bis-O-methylamidoxime, 2,8-diamidinodibenzothiophene, 2,8-bis(N-isopropylamidino)carbazole, 2,8-bis(N-hydroxyamidino)carbazole, 2,8-bis(2-imidazolinyl)dibenzothiophene, 2,8-bis(2-imidazolinyl)-5,5-dioxodibenzothiophene, 3,7-diamidinodibenzothiophene, 3,7-bis(N-isopropylamidino)dibenzothiophene, 3,7-bis(N-hydroxyamidino)dibenzothiophene, 3,7-diaminodibenzothiophene, 3,7-dibromodibenzothiophene, 3,7-dicyanodibenzothiophene, 2,8-diamidinodibenzofuran, 2,8-di(2-imidazolinyl)dibenzofuran, 2,8-di(N-isopropylamidino)dibenzofuran, 2,8-di(N-hydroxylamidino)dibenzofuran, 3,7-

di(2-imidazolinyl)dibenzofuran, 3,7-di(isopropylamidino)dibenzofuran, 3,7-di(N-hydroxylamidino)dibenzofuran, 2,8-dicyanodibenzofuran, 4,4'-dibromo-2,2'-dinitrobiphenyl, 2-methoxy-2'-nitro-4,4'-dibromobiphenyl, 2-methoxy-2'-amino-4,4'-dibromobiphenyl, 3,7-dibromodibenzofuran, 3,7-dicyanodibenzofuran, 2,5-bis(5-amidino-2-benzimidazolyl)pyrrole, 2,5-bis[5-(2-imidazolinyl)-2-benzimidazolyl]pyrrole, 2,6-bis[5-(2-imidazolinyl)-2-benzimidazolyl]pyridine, 1-methyl-2,5-bis(5-amidino-2-benzimidazolyl)pyrrole, 1-methyl-2,5-bis[5-(2-imidazolyl)-2-benzimidazolyl]pyrrole, 1-methyl-2,5-bis[5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-benzimidazolyl]pyrrole, 2,6-bis(5-amidino-2-benzimidazoyl)pyridine, 2,6-bis[5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-benzimidazolyl]pyridine, 2,5-bis(5-amidino-2-benzimidazolyl)furan, 2,5-bis-[5-(2-imidazolinyl)-2-benzimidazolyl]furan, 2,5-bis-(5-N-isopropylamidino-2-benzimidazolyl)furan, 2,5-bis-(4-guanylphenyl)furan, 2,5-bis(4-guanylphenyl)-3,4-dimethylfuran, 2,5-bis{p-[2-(3,4,5,6-tetrahydropyrimidyl)phenyl]}furan, 2,5-bis[4-(2-imidazolinyl)phenyl]furan, 2,5[bis-{4-(2-tetrahydropyrimidinyl)}phenyl]-3-(p-tolyloxy)furan, 2,5[bis{4-(2-imidazolinyl)}phenyl]-3-(p-tolyloxy)furan, 2,5-bis{4-[5-(N-2-aminoethylamido)benzimidazol-2-yl]phenyl}furan, 2,5-bis[4-(3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)phenyl]furan, 2,5-bis[4-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-yl)phenyl]furan, 2,5-bis(4-N,N-dimethylcarboxhydrazidephenyl)furan, 2,5-bis{4-[2-(N-2-hydroxyethyl)imidazolinyl]phenyl}furan, 2,5-bis[4-(N-isopropylamidino)phenyl]furan, 2,5-bis{4-[3-(dimethylaminopropyl)amidino]phenyl}furan, 2,5-bis{4-[N-(3-aminopropyl)amidino]phenyl}furan, 2,5-bis[2-(imidzaolinyl)phenyl]-3,4-bis(methoxymethyl)furan, 2,5-bis[4-N-(dimethylaminoethyl)guanyl]phenylfuran, 2,5-bis{4-[(N-2-hydroxyethyl)guanyl]phenyl}furan, 2,5-bis[4-N-(cyclopropylguanyl)phenyl]furan, 2,5-bis[4-(N,N-diethylaminopropyl)guanyl]phenylfuran, 2,5-bis{4-[2-(N-ethylimidazolinyl)]phenyl}furan, 2,5-bis{4-[N-(3-pentylguanyl)]}phenylfuran,

2,5-bis[4-(2-imidazolinyl)phenyl]-3-methoxyfuran, 2,5-bis[4-(N-isopropylamidino)phenyl]-3-methylfuran, bis[5-amidino-2-benzimidazolyl]methane, bis[5-(2-imidazolyl)-2-benzimidazolyl]methane, 1,2-bis[5-amidino-2-benzimidazolyl]ethane, 1,2-bis[5-(2-imidazolyl)-2-benzimidazolyl]ethane, 1,3-bis[5-amidino-2-benzimidazolyl]propane, 1,3-bis[5-(2-imidazolyl)-2-benzimidazolyl]propane, 1,4-bis[5-amidino-2-benzimidazolyl]propane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]butane, 1,8-bis[5-amidino-2-benzimidazolyl]octane, trans-1,2-bis[5-amidino-2-benzimidazolyl]ethene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-methylbutane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-ethylbutane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-methyl-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1,3-butadiene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-methyl-1,3-butadiene, bis[5-(2-pyrimidyl)-2-benzimidazolyl]methane, 1,2-bis[5-(2-pyrimidyl)-2-benzimidazolyl]ethane, 1,3-bis[5-amidino-2-benzimidazolyl]propane, 1,3-bis[5-(2-pyrimidyl)-2-benzimidazolyl]propane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]butane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-methylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-ethylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-methyl-1-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1,3-butadiene, and 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-methyl-1,3-butadiene, 2,4-bis(4-guanylphenyl)pyrimidine, 2,4-bis(4-imidazolin-2-yl)pyrimidine, 2,4-bis[(tetrahydropyrimidinyl-2-yl)phenyl]pyrimidine, 2-(4-[N-i-propylguanyl]phenyl)-4-(2-methoxy-4-[N-i-propylguanyl]phenyl)pyrimidine, 4-(N-cyclopentylamidino)-1,2-phenylene diamine, 2,5-bis-[2-(5-amidino)benzimidazoyl]furan, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]furan,

2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]furan, 2,5-bis[2-(5-amidino)benzimidazoyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]pyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]pyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]pyrrole, 1-methyl-2,5-bis[2-(5-amidino)benzimidazoyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]-1-methylpyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]-1-methylpyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]thiophene, 2,6-bis[2-{5-(2-imidazolino)}benzimidazoyl]pyridine, 2,6-bis[2-(5-amidino)benzimidazoyl]pyridine, 4,4'-bis[2-(5-N-isopropylamidino)benzimidazoyl]-1,2-diphenylethane, 4,4'-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]-2,5-diphenylfuran, 2,5-bis[2-(5-amidino)benzimidazoyl]benzo[b]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]benzo[b]furan, 2,7-bis[2-(5-N-isopropylamidino)benzimidazoyl]fluorine, 2,5-bis[4-(3-(N-morpholinopropyl)carbamoyl)phenyl]furan, 2,5-bis[4-(2-N,N-dimethylaminoethylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N,N-dimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N-methyl-3-N-phenylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N, N^8,N^{11}-trimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[3-amidinophenyl]furan, 2,5-bis[3-(N-isopropylamidino)amidinophenyl]furan, 2,5-bis[3[(N-(2-dimethylaminoethyl)amidino]phenylfuran, 2,5-bis[4-(N-2,2,2-trichloroethoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-thioethylcarbonyl) amidinophenyl]furan, 2,5-bis[4-(N-benzyloxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-fluoro)-phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-methoxy)phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4(1-

acetoxyethoxycarbonyl)amidinophenyl]furan, and 2,5-bis[4-(N-(3-fluoro)phenoxycarbonyl)amidinophenyl]furan, or a salt of any of the above.

Alternatively, the second compound can be a functional analog of pentamidine, such as netropsin, distamycin, bleomycin, actinomycin, daunorubicin, or a compound that falls within a formula provided in any of U.S. Patent Nos. 5,428,051; 5,521,189; 5,602,172; 5,643,935; 5,723,495; 5,843,980; 6,008,247; 6,025,398; 6,172,104; 6,214,883; and 6,326,395, or U.S. Patent Application Publication Nos. US 2001/0044468 A1 and US 2002/0019437 A1.

The methods of the invention can include administration to a patient a compound of formula (I) and a compound of formula (II) by intravenous, intramuscular, inhalation, rectal, or oral administration.

In another aspect, the invention features a method for treating a patient having a neoplasm such as cancer by the method of either the first or second aspect that further includes administration to the patient an additional treatment for cancer, with the additional treatment and the treatment of the first or second aspect administered within six months of each other. The additional treatment can be surgery, radiation therapy, chemotherapy, immunotherapy, anti-angiogenesis therapy, or gene therapy. Preferably, the additional treatment is chemotherapy with an antiproliferative agent. Most preferably, the additional treatment includes administering to a patient a Group A anti-proliferative agent, as defined below. Preferred agents include bleomycin, carmustine, cisplatin, daunorubicin, etoposide, melphalan, mercaptopurine, methotrexate, mitomycin, vinblastine, paclitaxel, docetaxel, vincristine, vinorelbine, cyclophosphamide, chlorambucil, gemcitabine, capecitabine, 5-fluorouracil, fludarabine, raltitrexed, irinotecan, topotecan, doxorubicin, epirubicin, letrozole, anastrazole, formestane, exemestane, tamoxifen, toremofine, goserelin, leuporelin, bicalutamide, flutamide, nilutamide, hypericin, trastuzumab, or rituximab, or any combination thereof.

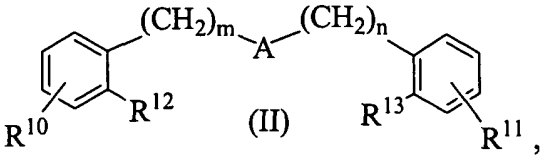
When the additional treatment is a chemotherapy, it and a compound of formulas (I) and a compound of formula (II) can be administered within 14 days of

each other. Preferably, all treatments of the third aspect are administered within ten days of each other, more preferably within five days of each other, and most preferably within twenty-four hours of each other or even simultaneously.

Cancers treated according to any of the methods of the invention can be, for example, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma. Preferably, the cancer being treated is lung cancer, especially lung cancer attributed to squamous cell carcinoma, adenocarinoma, or large cell carcinoma, colorectal cancer, ovarian cancer, especially ovarian adenocarcinoma, or prostate cancer.

In another aspect, the invention features a method for treating a patient who has a neoplasm, or inhibiting the development of a neoplasm in a patient who is at risk for developing a neoplasm by administering to the patient a pharmaceutical composition that includes a compound of formula (I), a compound of formula (II), and a pharmaceutically acceptable carrier.

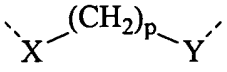
In one embodiment, the compound of formula (II) is



(II),

or a pharmaceutically acceptable salt thereof,

wherein A is



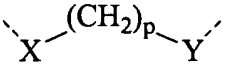
,

each of X and Y is independently O or NH;

p is an integer between 2 and 6, inclusive; and

m and n are, independently, integers between 0 and 2, inclusive, wherein the sum of m and n is greater than 0;

or A is

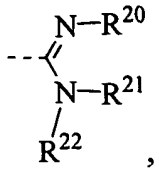


,

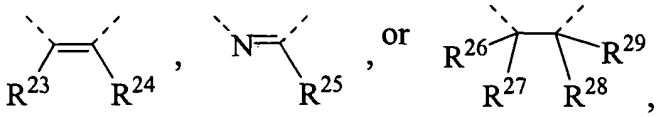
each of X and Y is independently O or NH,

each of m and n is 0, and

each of R^{10} and R^{11} is, independently, selected from the group represented by

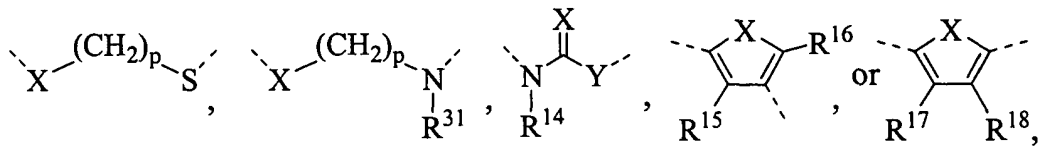


wherein R^{21} is C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, carbo(C_1-C_6 alkoxy), carbo(C_6-C_{18} aryl C_1-C_6 alkoxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



wherein each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, and R^{28} is, independently, H or C_1-C_6 alkyl, and R^{29} is C_1-C_6 alkyl, C_1-C_6 alkyloxy, or trifluoromethyl;

or A is



each of X and Y is, independently, O, NR^{19}, or S,

each of R^{14} and R^{19} is, independently, H or C_1-C_6 alkyl,

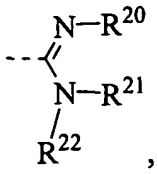
each of R^{15}, R^{16}, R^{17}, and R^{18} is, independently, H, C_1-C_6 alkyl, halogen, C_1-C_6 alkyloxy, C_6-C_{18} aryloxy, or C_6-C_{18} aryl C_1-C_6 alkyloxy,

R^{31} is C_1-C_6 alkyl,

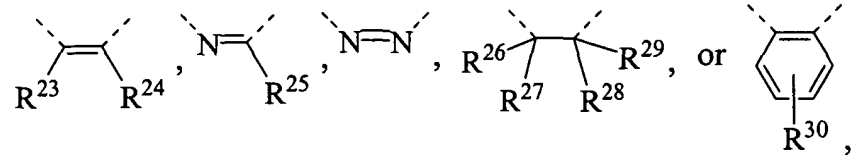
p is an integer between 2 and 6, inclusive,

each of m and n is, independently, an integer between 0 and 2, inclusive,

each of R^{10} and R^{11} is, independently, selected from the group represented by



wherein R^{21} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, carbo(C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryl C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



wherein each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, R^{28}, and R^{29} are, independently, H or C_1-C_6 alkyl, and R^{30} is H, halogen, trifluoromethyl, OCF_3, NO_2, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl..

Methods of the invention can include administration to a patient a compound of formula (I) and a compound of formula (II) by intravenous, intramuscular, inhalation, rectal, or oral administration. These compounds are present in amounts that, when administered together to a patient having a neoplasm, reduce cell proliferation in the neoplasm.

In another aspect, the invention features a method for treating a patient who has a neoplasm, or inhibiting the development of a neoplasm in a patient who is at risk for developing a neoplasm. The method includes administration to a patient an inhibitor of protein kinase C and a compound of formula (II). In one

embodiment, this method can further include administering to the patient one or more Group A antiproliferative agents.

In another aspect, the invention features a method for treating a patient who has a neoplasm, or inhibiting the development of a neoplasm in a patient who is at risk for developing a neoplasm. The method includes administration to a patient a compound of formula (I) and an endo-exonuclease inhibitor. In one embodiment, this method can further include administering to the patient one or more Group A antiproliferative agents.

In yet another aspect, the invention features a method for treating a patient who has a neoplasm, or inhibiting the development of a neoplasm in a patient who is at risk for developing a neoplasm. The method includes administration to a patient a compound of formula (I) and a PRL phosphatase inhibitor or a PTP1B inhibitor. In one embodiment, this method can further include administering to the patient one or more Group A antiproliferative agents.

In the combination therapies of the invention, the therapy components are administered simultaneously, or within 14 days of each other, in amounts sufficient to inhibit the growth of said neoplasm.

Combination therapy may be provided wherever chemotherapy is performed: at home, the doctor's office, a clinic, a hospital's outpatient department, or a hospital. Treatment generally begins at a hospital so that the doctor can observe the therapy's effects closely and make any adjustments that are needed. The duration of the combination therapy depends on the kind of cancer being treated, the age and condition of the patient, the stage and type of the patient's disease, and how the patient's body responds to the treatment. Drug administration may be performed at different intervals (e.g., daily, weekly, or monthly) and the administration of each agent can be determined individually. Combination therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to build healthy new cells and regain its strength.

Depending on the type of cancer and its stage of development, the combination therapy can be used to treat cancer, to slow the spreading of the cancer, to slow the cancer's growth, to kill or arrest cancer cells that may have spread to other parts of the body from the original tumor, to relieve symptoms caused by the cancer, or to prevent cancer in the first place. Combination therapy can also help people live more comfortably by eliminating cancer cells that cause pain or discomfort.

The administration of a combination of the present invention allows for the administration of lower doses of each compound, providing similar efficacy and lower toxicity compared to administration of either compound alone. Alternatively, such combinations result in improved efficacy in treating neoplasms with similar or reduced toxicity.

As used herein, the terms "cancer" or "neoplasm" or "neoplastic cells" is meant a collection of cells multiplying in an abnormal manner. Cancer growth is uncontrolled and progressive, and occurs under conditions that would not elicit, or would cause cessation of, multiplication of normal cells.

By "inhibits the growth of a neoplasm" is meant measurably slows, stops, or reverses the growth rate of the neoplasm or neoplastic cells *in vitro* or *in vivo*. Desirably, a slowing of the growth rate is by at least 20%, 30%, 50%, or even 70%, as determined using a suitable assay for determination of cell growth rates (e.g., a cell growth assay described herein). Typically, a reversal of growth rate is accomplished by initiating or accelerating necrotic or apoptotic mechanisms of cell death in the neoplastic cells, resulting in a shrinkage of the neoplasm.

By "an effective amount" is meant the amount of a compound, in a combination according to the invention, required to inhibit the growth of the cells of a neoplasm *in vivo*. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of neoplasms (i.e., cancer) varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian

will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain saturated or unsaturated groups, and of cyclic groups, i.e., cycloalkyl and cycloalkenyl groups. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, and adamantyl groups.

By "carbo(C_1-C_6 alkoxy)" is meant an ester fragment of the structure CO_2R, wherein R is an alkyl group.

By "carbo(C_6-C_{18} aryl-C_1-C_6 alkoxy)" is meant an ester fragment of the structure CO_2R, wherein R is an alkaryl group.

By "aryl" is meant a C_6-C_{18} carbocyclic aromatic ring or ring system. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl, and indenyl groups. The term "heteroaryl" means a C_1- C_9 aromatic ring or ring systems that contains at least one ring heteroatom (e.g., O, S, N). Heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, tetrazolyl, and imidazolyl groups.

By "halide" or "halogen" is meant bromine, chlorine, iodine, or fluorine.

By "heterocycle" is meant a C_1- C_9 non-aromatic ring or ring system that contains at least one ring heteroatom (e.g., O, S, N). Heterocycles include, for example, pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiazolidinyl, and imidazolidinyl groups.

Aryl, heteroaryl, and heterocycle groups may be unsubstituted or substituted by one or more substituents selected from the group consisting of C_{1-6} alkyl, hydroxy, halo, nitro, C_{1-6} alkoxy, C_{1-6} alkylthio, trihalomethyl, C_{1-7} acyl, carbonyl, heteroarylcarbonyl, nitrile, C_{1-6} alkoxycarbonyl, oxo, alkyl (wherein the alkyl group has from 1 to 6 carbon atoms) and heteroarylalkyl (wherein the alkyl group has from 1 to 6 carbon atoms).

By "non-vicinal O, S, or N" is meant an oxygen, sulfur, or substituted or unsubstituted nitrogen heteroatom substituent in a linkage, wherein the heteroatom substituent does not form a bond to a saturated carbon that is bonded to another heteroatom.

By "endo-exonuclease inhibitor" is meant a compound that inhibits (e.g., by at least 10%, 20%, 30%, or more) the enzymatic activity of an enzyme having endo-exonuclease activity. Such inhibitors include, but are not limited to, pentamidine, pentamidine analogs, and pentamidine metabolites.

By a "low dosage" is meant at least 10% less than the lowest standard recommended dosage of an anti-proliferative agent as recommended by the *Physician's Desk Reference*, 57th Edition (2003). By a "high dosage" is meant at least 5% more than the highest standard dosage of an anti-proliferative agent. By a "moderate dosage" is meant the dosage between the low dosage and the high dosage.

By "phosphatase of regenerating liver inhibitor" is meant a compound that inhibits (e.g., by at least 10%, 20%, 30%, or more) the enzymatic activity of a member of the phosphatase of regenerating liver (PRL) family of tyrosine phosphatases. Members of this family include, but are not limited to, PRL-1, PRL-2, and PRL-3. Inhibitors include, but are not limited to, pentamidine, pentamidine analogs, and pentamidine metabolites.

By "protein tyrosine phosphatase 1B inhibitor" is meant a compound that inhibits (e.g., by at least 10%, 20%, 30%, or more) the enzymatic activity of protein phosphatase 1B. Inhibitors include, but are not limited to, pentamidine, pentamidine analogs, and pentamidine metabolites.

By an "antiproliferative agent" is meant a compound that, individually, inhibits the growth of a neoplasm. Antiproliferative agents of the invention include alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors,

pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists and antagonists, endothelin A receptor antagonists, retinoic acid receptor agonists, immunomodulators, hormonal and antihormonal agents, photodynamic agents, and tyrosine kinase inhibitors. Antiproliferative agents that can be administered in combination with any compound having formula (I) and any compound having formula (II) for treating a neoplasm

By "Group A antiproliferative agent" is meant an agent listed in Table 1.

Table 1.

Alkylating agents	cyclophosphamide busulfan ifosfamide melphalan hexamethylmelamine thiotepa chlorambucil dacarbazine carmustine	lomustine procarbazine altretamine estramustine phosphate mechlorethamine streptozocin temozolomide semustine.
Platinum agents	cisplatin oxaliplatin spiroplatinum, carboxyphthalatoplatinum, tetraplatin ormiplatin iproplatin	carboplatinum ZD-0473 (AnorMED) lobaplatin (Aeterna) satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
Antimetabolites	azacytidine gemcitabine capecitabine 5-fluorouracil floxuridine 2-chlorodeoxyadenosine 6-mercaptopurine 6-thioguanine cytarabin 2-fluorodeoxy cytidine methotrexate idatrexate	tomudex trimetrexate deoxycoformycin fludarabine pentostatin raltitrexed hydroxyurea decitabine (SuperGen) clofarabine (Bioenvision) irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) ethynylcytidine (Taiho)

Table 1 (cont.)

Topoisomerase inhibitors	amsacrine epirubicin etoposide teniposide or mitoxantrone irinotecan (CPT-11) 7-ethyl-10-hydroxy-camptothecin topotecan dexrazoxanet (TopoTarget) pixantrone (Novuspharma) rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharma)	rubitecan (SuperGen) exatecan mesylate (Daiichi) quinamed (ChemGenex) gimatecan (Sigma-Tau) diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
Antitumor antibiotics	dactinomycin (actinomycin D) doxorubicin (adriamycin) deoxyrubicin valrubicin daunorubicin (daunomycin) epirubicin therarubicin idarubicin rubidazone plicamycinp porfiromycin cyanomorpholinodoxorubicin mitoxantrone (novantrone)	amonafide azonafide anthrapyrazole oxantrazole losoxantrone bleomycin sulfate (blenoxane) bleomycinic acid bleomycin A bleomycin B mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
Antimitotic agents	paclitaxel docetaxel colchicine vinblastine vincristine vinorelbine vindesine dolastatin 10 (NCI) rhizoxin (Fujisawa) mivobulin (Warner-Lambert) cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) cryptophycin 52 (Eli Lilly) vinflunine (Fabre) auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) taxoprexin (Protarga)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTAMedica) ER-86526 (Eisai) combretastatin A4 (BMS) isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) azaepothilone B (BMS) BNP-7787 (BioNumerik) CA-4 prodrug (OXiGENE) dolastatin-10 (NIH) CA-4 (OXiGENE)

Table 1 (cont.)

Aromatase inhibitors	aminoglutethimide letrozole anastrazole formestane	exemestane atamestane (BioMedicines) YM-511 (Yamanouchi)
Thymidylate synthase inhibitors	pemetrexed (Eli Lilly) ZD-9331 (BTG)	nolatrexed (Eximias) CoFactor™ (BioKeys)
DNA antagonists	trabectedin (PharmaMar) glufosfamide (Baxter International) albumin + 32P (Isotope Solutions) thymectacin (NewBiotics) edotreotide (Novartis)	mafosfamide (Baxter International) apaziquone (Spectrum Pharmaceuticals) O6 benzyl guanine (Paligent)
Farnesyltransferase inhibitors	arglabin (NuOncology Labs) lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	tipifarnib (Johnson & Johnson) perillyl alcohol (DOR BioPharma)
Pump inhibitors	CBT-1 (CBA Pharma) tariquidar (Xenova) MS-209 (Schering AG)	zosuquidar trihydrochloride (Eli Lilly) biricodar dicitrate (Vertex)
Histone acetyltransferase inhibitors	tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	pivaloyloxymethyl butyrate (Titan) depsipeptide (Fujisawa)
Metalloproteinase inhibitors	Neovastat (Aeterna Laboratories) marimastat (British Biotech)	CMT-3 (CollaGenex) BMS-275291 (Celltech)
Ribonucleoside reductase inhibitors	gallium maltolate (Titan) triapine (Vion)	tezacitabine (Aventis) didox (Molecules for Health)
TNF alpha agonists/antagonists	virulizin (Lorus Therapeutics) CDC-394 (Celgene)	revimid (Celgene)
Endothelin A receptor antagonist	atrasentan (Abbott) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
Retinoic acid receptor agonists	fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	alitretinoin (Ligand)
Immuno-modulators	interferon oncophage (Antigenics) GMK (Progenics) adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) IRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) synchrovax vaccines (CTL Immuno) melanoma vaccine (CTL Immuno) p21 RAS vaccine (GemVax)	dexosome therapy (Anosys) pentrix (Australian Cancer Technology) ISF-154 (Tragen) cancer vaccine (Intercell) norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) ß-alethine (Dovetail) CLL therapy (Vasogen)

Table 1 (cont.)

Hormonal and antihormonal agents	estrogens conjugated estrogens ethinyl estradiol chlortrianisen idenestrol hydroxyprogesterone caproate medroxyprogesterone testosterone testosterone propionate; fluoxymesterone methyltestosterone diethylstilbestrol megestrol tamoxifen toremofine dexamethasone	prednisone methylprednisolone prednisolone aminoglutethimide leuprolide goserelin leuporelin bicalutamide flutamide octreotide nilutamide mitotane P-04 (Novogen) 2-methoxyestradiol (EntreMed) arzoxifene (Eli Lilly)
Photodynamic agents	talaporfin (Light Sciences) Theralux (Theratechnologies) motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) lutetium texaphyrin (Pharmacyclics) hypericin
Tyrosine Kinase Inhibitors	imatinib (Novartis) leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) erlotinib (Oncogene Science) canertinib (Pfizer) squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmithKline) EKB-509 (Wyeth) EKB-569 (Wyeth)	kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) phenoxodiol () trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)

Table 1 (cont.)

Miscellaneous agents	
SR-27897 (CCK A inhibitor, Sanofi-Synthelabo)	BCX-1777 (PNP inhibitor, BioCryst)
tocladesine (cyclic AMP agonist, Ribapharm)	ranpirnase (ribonuclease stimulant, Alfacell)
alvocidib (CDK inhibitor, Aventis)	galarubicin (RNA synthesis inhibitor, Dong-A)
CV-247 (COX-2 inhibitor, Ivy Medical)	tirapazamine (reducing agent, SRI International)
P54 (COX-2 inhibitor, Phytopharm)	N-acetylcysteine (reducing agent, Zambon)
CapCell™ (CYP450 stimulant, Bavarian Nordic)	R-flurbiprofen (NF-kappaB inhibitor, Encore)
GCS-100 (gal3 antagonist, GlycoGenesys)	3CPA (NF-kappaB inhibitor, Active Biotech)
G17DT immunogen (gastrin inhibitor, Aphton)	seocalcitol (vitamin D receptor agonist, Leo)
efaproxiral (oxygenator, Allos Therapeutics)	131-I-TM-601 (DNA antagonist, TransMolecular)
PI-88 (heparanase inhibitor, Progen)	eflornithine (ODC inhibitor , ILEX Oncology)
tesmilifene (histamine antagonist, YM BioSciences)	minodronic acid (osteoclast inhibitor, Yamanouchi)
histamine (histamine H2 receptor agonist, Maxim)	indisulam (p53 stimulant, Eisai)
tiazofurin (IMPDH inhibitor, Ribapharm)	aplidine (PPT inhibitor, PharmaMar)
cilengitide (integrin antagonist, Merck KGaA)	rituximab (CD20 antibody, Genentech)
SR-31747 (IL-1 antagonist, Sanofi-Synthelabo)	gemtuzumab (CD33 antibody, Wyeth Ayerst)
CCI-779 (mTOR kinase inhibitor, Wyeth)	PG2 (hematopoiesis enhancer, Pharmagenesis)
exisulind (PDE V inhibitor, Cell Pathways)	Immunol™ (triclosan oral rinse, Endo)
CP-461 (PDE V inhibitor, Cell Pathways)	triacetyluridine (uridine prodrug , Wellstat)
AG-2037 (GART inhibitor, Pfizer)	SN-4071 (sarcoma agent, Signature BioScience)
WX-UK1 (plasminogen activator inhibitor, Wilex)	TransMID-107™ (immunotoxin, KS Biomedix)
PBI-1402 (PMN stimulant, ProMetic LifeSciences)	PCK-3145 (apoptosis promotor, Procyon)
bortezomib (proteasome inhibitor, Millennium)	doranidazole (apoptosis promotor, Pola)
SRL-172 (T cell stimulant, SR Pharma)	CHS-828 (cytotoxic agent, Leo)
TLK-286 (glutathione S transferase inhibitor, Telik)	trans-retinoic acid (differentiator, NIH)
PT-100 (growth factor agonist, Point Therapeutics)	MX6 (apoptosis promotor, MAXIA)
midostaurin (PKC inhibitor, Novartis)	apomine (apoptosis promotor, ILEX Oncology)
bryostatin-1 (PKC stimulant, GPC Biotech)	urocidin (apoptosis promotor, Bioniche)
CDA-II (apoptosis promotor, Everlife)	Ro-31-7453 (apoptosis promotor, La Roche)
SDX-101 (apoptosis promotor, Salmedix)	brostallicin (apoptosis promotor, Pharmacia)
ceflatonin (apoptosis promotor, ChemGenex)	

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, thereof, as well as racemic mixtures of the compounds described herein.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Drawings

FIG. 1 is a chart demonstrating the effectiveness of a chlorpromazine/pentamidine combination (5 mg/Kg chlorpromazine and 20

mg/Kg pentamidine) administered to female SCID mice that have A549 human lung tumor xenografts.

FIG. **2** is a chart demonstrating the effectiveness of a chlorpromazine/pentamidine combination (5 mg/Kg chlorpromazine and 20 mg/Kg pentamidine) administered to male SCID mice that have A549 human lung tumor xenografts, with treatment consisting of a three week treatment period, followed by a one week no-treatment period, followed by a two week treatment period.

Detailed Description

We have discovered that the combination of the antipsychotic drug chlorpromazine and the antiprotozoal drug pentamidine (heretofore referred to as "C/P combination") exhibits substantial antiproliferative activity against cancer cells, and that the concentrations that exhibited maximal antiproliferative activity against cancer cells were not toxic to normal cells.

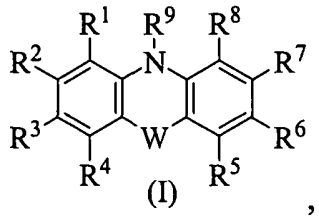
When used in concert with an anti-proliferative agent, the C/P combination may also enhance the efficacy of the anti-proliferative agent such that the dosage of the anti-proliferative compound is lowered to achieve the same therapeutic benefit, thereby moderating any unwanted side effects. Preferably, a moderate dose, and most preferably, a low dose of the anti-proliferative agent would be used in such a case. Alternatively, the C/P combination may be used to augment the efficacy of an anti-proliferative compound at its normal dose, such that an increased therapeutic benefit is obtained. In addition, when used with an anti-proliferative agent, the C/P combination may be useful in improving the ability of that agent to overcome neoplasm drug resistance. Thus, the C/P combination is useful for the treatment of cancer and other neoplasms and may find further benefit when used with an anti-proliferative agent.

Based on known properties that are shared between chlorpromazine and its analogs and metabolites, and between pentamidine and its analogs and

metabolites, it is likely that structurally related compounds can be substituted for chlorpromazine and/or pentamidine in the antiproliferative combinations of the invention. Information regarding each of the drugs and its analogs and metabolites is provided below.

Phenothiazines

Phenothiazines that are useful in the antiproliferative combination of the invention as chlorpromazine analogs are compounds having the general formula (I):

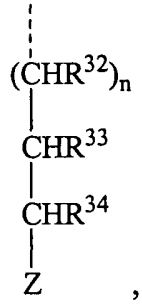


(I) ,

or a pharmaceutically acceptable salt thereof,

wherein R^2 is selected from the group consisting of: CF_3, halo, OCH_3, $COCH_3$, CN, OCF_3, $COCH_2CH_3$, $CO(CH_2)_2CH_3$, and SCH_2CH_3;

R^9 has the formula:

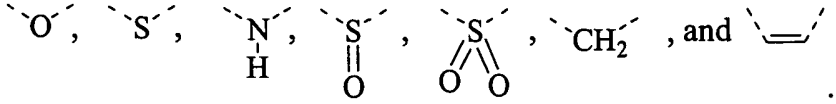


,

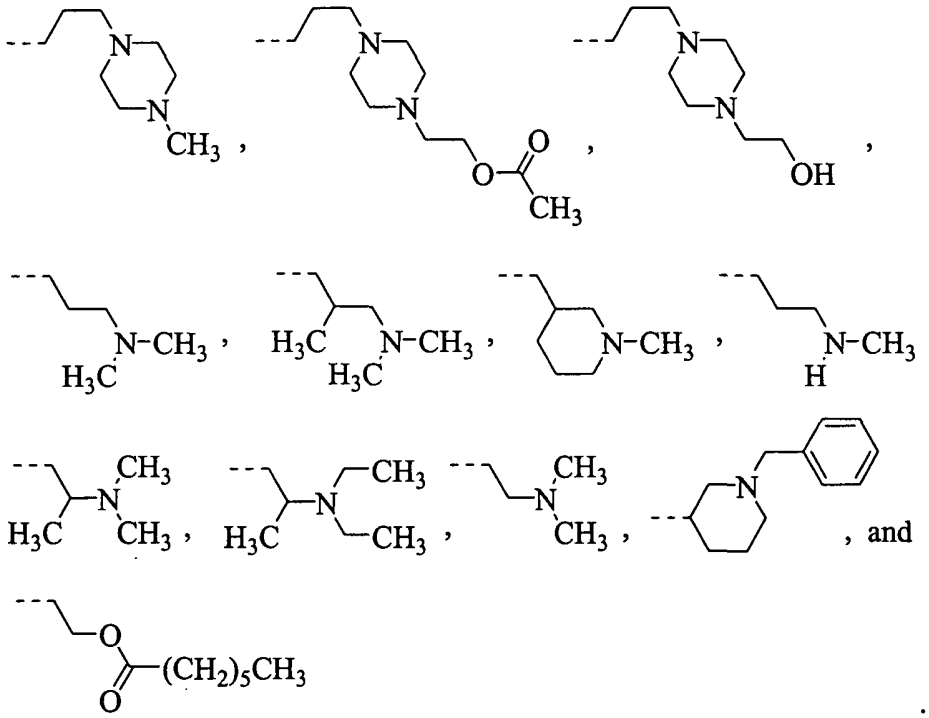
wherein n is 0 or 1, each of R^{32}, R^{33}, and R^{34} is, independently, H or substituted or unsubstituted C_{1-6} alkyl, and Z is $NR^{35}R^{36}$ or OR^{37}, wherein each of R^{35} and R^{36} is, independently, H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkaryl, substituted or unsubstituted alkheteroaryl, and R^{37} is H, C_{1-6} alkyl, or C_{1-7} acyl, wherein any of R^{33}, R^{34}, R^{35}, and R^{36} can be optionally taken together with intervening carbon or non-vicinal O, S, or N atoms to form one or

more five- to seven-membered rings, substituted with one or more hydrogens, substituted or unsubstituted C_{1-6} alkyl groups, C_{6-12} aryl groups, alkoxy groups, halogen groups, substituted or unsubstituted alkaryl groups, or substituted or unsubstituted alkheteroaryl groups;

each of R^1, R^3, R^4, R^5, R^6, R^7, and R^8 is independently H, OH, F, OCF_3, or OCH_3; and W is selected from the group consisting of:

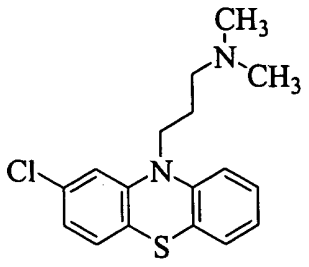


In preferred compounds, R_2 is Cl; each of R_1, R_3, R_4, R_5, R_6, R_7, R_8 is H or F; and R^9 is selected from the group consisting of:



More preferably, each of R_1, R_4, R_5, R_6, and R_8 is H.

The most commonly prescribed member of the phenothiazine family is chlorpromazine, which has the structure:



Chlorpromazine is currently available in the following forms: tablets, capsules, suppositories, oral concentrates and syrups, and formulations for injection.

Phenothiazines considered to be chlorpromazine analogs include fluphenazine, prochlorperazine, promethazine, thioridazine, and trifluoperazine. Many of these share antipsychotic or antiemetic activity with chlorpromazine. Also included as chlorpromazine analogs are those compounds in PCT Application WO/02057244, which is hereby incorporated by reference.

Phenothiazines are thought to elicit their antipsychotic and antiemetic effects via interference with central dopaminergic pathways in the mesolimbic and medullary chemoreceptor trigger zone areas of the brain. Extrapyramidal side effects are a result of interactions with dopaminergic pathways in the basal ganglia. Although often termed dopamine blockers, the exact mechanism of dopaminergic interference responsible for the drugs' antipsychotic activity has not been determined.

Phenothiazines are also known to inhibit the activity of protein kinase C. Protein kinase C mediates the effects of a large number of hormones and is involved in may aspects of cellular regulation and carcinogenesis (Castagna, et al., *J. Biol. Chem.* 1982, 257:7847-51). The enzyme is also thought to play a role in certain types of resistance to cancer chemotherapeutic agents. Chlorpromazine has been investigated for the inhibition of protein kinase C both *in vitro* (Aftab, et al., Mol. Pharmacology, 1991, 40:798-805) and *in vivo* (Dwivedi, et al., *J. Pharm. Exp. Ther.*, 1999, 291:688-704).

Chlorpromazine also has strong alpha-adrenergic blocking activity and can cause orthostatic hypotension. Chlorpromazine also has moderate anticholinergic activity manifested as occasional dry mouth, blurred vision, urinary retention, and constipation. Chlorpromazine increases prolactin secretion owing to its dopamine receptor blocking action in the pituitary and hypothalamus.

Chlorpromazine is readily absorbed from the gastrointestinal tract. Its bioavailability is variable due to considerable first pass metabolism by the liver. Liquid concentrates may have greater bioavailability than tablets. Food does not appear to affect bioavailability consistently. I.m. administration bypasses much of the first pass effect and higher plasma concentrations are achieved. The onset of action after i.m. administration is usually 15 to 30 minutes and after oral administration 30 to 60 minutes. Rectally administered chlorpromazine usually takes longer to act than orally administered chlorpromazine.

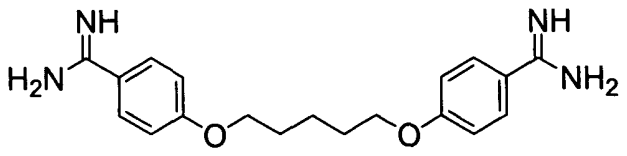
Chlorpromazine Metabolites

Because chlorpromazine undergoes extensive metabolic transformation into a number of metabolites that may be therapeutically active, these metabolites may be substituted from chlorpromazine in the antiproliferative combination of the invention. The metabolism of chlorpromazine yields, for example, oxidative N-demethylation to yield the corresponding primary and secondary amine, aromatic oxidation to yield a phenol, N-oxidation to yield the N-oxide, S-oxidation to yield the sulphoxide or sulphone, oxidative deamination of the aminopropyl side chain to yield the phenothiazine nuclei, and glucuronidation of the phenolic hydroxy groups and tertiary amino group to yield a quaternary ammonium glucuronide.

In other examples of chlorpromazine metabolites useful in the antiproliferative combination of the invention, each of positions 3, 7, and 8 of the phenothiazine can independently be substituted with a hydroxyl or methoxyl moiety.

Pentamidine

Pentamidine is currently used for the treatment of *Pneumocystis carinii*, *Leishmania donovani*, *Trypanosoma brucei*, *T. gambiense*, and *T. rhodesiense* infections. The structure of pentamidine is:



It is available formulated for injection or inhalation. For injection, pentamidine is packaged as a nonpyrogenic, lyophilized product. After reconstitution, it is administered by intramuscular or intravenous injection.

Pentamidine isethionate is a white, crystalline powder soluble in water and glycerin and insoluble in ether, acetone, and chloroform. It is chemically designated 4,4'- diamidino-diphenoxypentane di(β-hydroxyethanesulfonate). The molecular formula is $C_{23}H_{36}N_4O_{10}S_2$ and the molecular weight is 592.68.

The mode of action of pentamidine is not fully understood. *In vitro* studies with mammalian tissues and the protozoan *Crithidia oncopelti* indicate that the drug interferes with nuclear metabolism, producing inhibition of the synthesis of DNA, RNA, phospholipids, and proteins. Several lines of evidence suggest that the action of pentamidine against leishmaniasis, a tropical disease caused by a protozoan residing in host macrophages, might be mediated via host cellular targets and the host immune system. Pentamidine selectively targets intracellular leishmania in macrophages but not the free-living form of the protozoan and has reduced anti-leishmania activity in immunodeficient mice in comparison with its action in immunocompetent hosts.

Recently, pentamidine was shown to be an effective inhibitor of protein tyrosine phosphatase 1B (PTP1B). Because PTP1B dephosphorylates and inactivates Jak kinases, which mediate signaling of cytokines with leishmanicidal

activity, its inhibition by pentamidine might result in augmentation of cytokine signaling and anti-leishmania effects. Pentamidine has also been shown to be a potent inhibitor of the oncogenic phosphatases of regenerating liver (PRL). Pentamidine has also been shown to inhibit the activity of endo-exonuclease (PCT Publication No. WO 01/35935). Thus, in the methods of the invention, pentamidine can be replaced by any PTP1B inhibitor, PRL inhibitor, or endo-exonuclease inhibitor.

Little is known about the drug's pharmacokinetics. In seven patients treated with daily intramuscular doses of pentamidine at 4 mg/kg for 10 to 12 days, plasma concentrations were between 0.3 and 0.5 μg/mL. The patients continued to excrete decreasing amounts of pentamidine in urine up to six to eight weeks after cessation of the treatment.

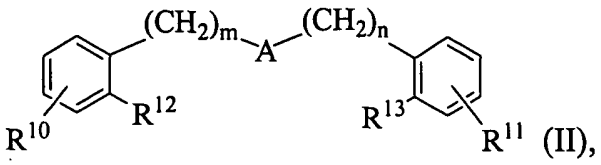
Tissue distribution of pentamidine has been studied in mice given a single intraperitoneal injection of pentamidine at 10 mg/kg. The concentration in the kidneys was the highest, followed by that in the liver. In mice, pentamidine was excreted unchanged, primarily via the kidneys with some elimination in the feces. The ratio of amounts excreted in the urine and feces (4:1) was constant over the period of study.

Pentamidine Analogs

Aromatic diamidino compounds can replace pentamidine in the antiproliferative combination of the invention. Aromatic diamidino compounds such as propamidine, butamidine, heptamidine, and nonamidine share properties with pentamidine in that they exhibit antipathogenic or DNA binding properties. Other analogs (e.g., stilbamidine and indole analogs of stilbamidine, hydroxystilbamidine, diminazene, benzamidine, 4,4'-(pentamethylenedioxy)phenamidine, dibrompropamidine, 1,3-bis(4-amidino-2-methoxyphenoxy)propane (DAMP), netropsin, distamycin, phenamidine, amicarbalide, bleomycin, actinomycin, and daunorubicin) also exhibit properties

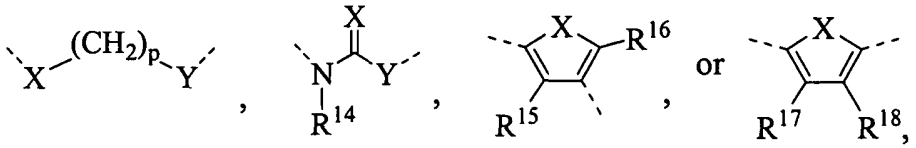
similar to those of pentamidine. It is likely that these compounds will have anti-cancer activity when administered in combination with chlorpromazine (or an analog or metabolite of chlorpromazine).

Pentamidine analogs are described, for example, by formula (II)



(II),

wherein A is



wherein

each of X and Y is, independently, O, NR^{19}, or S,

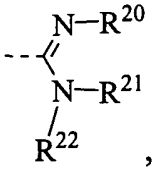
each of R^{14} and R^{19} is, independently, H or C_1-C_6 alkyl,

each of R^{15}, R^{16}, R^{17}, and R^{18} is, independently, H, C_1-C_6 alkyl, halogen, C_1-C_6 alkyloxy,C_6-C_{18} aryloxy, or C_6-C_{18} aryl-C_1-C_6 alkyloxy,

p is an integer between 2 and 6, inclusive,

each of m and n is, independently, an integer between 0 and 2, inclusive,

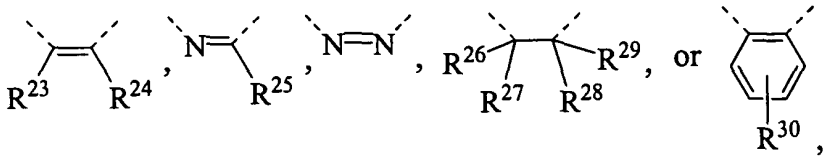
each of R^{10} and R^{11} is



wherein

R^{21} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy-C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl, R^{22} is H, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkyloxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl,

carbo(C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryl C_1-C_6 alkyloxy), carbo(C_6-C_{18} aryloxy), or C_6-C_{18} aryl, and R^{20} is H, OH, or C_1-C_6 alkyloxy, or R^{20} and R^{21} together represent



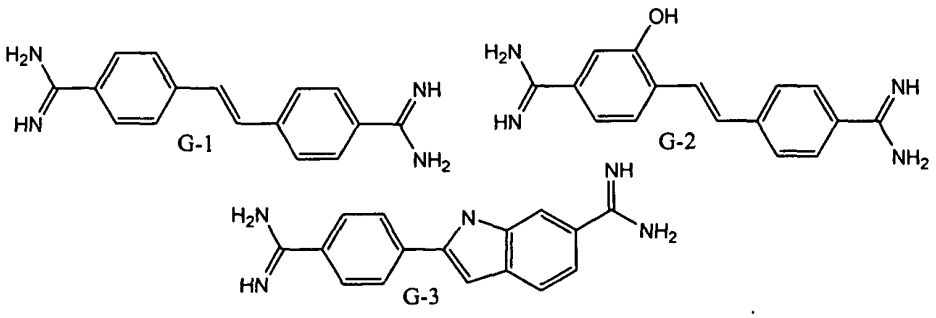
wherein

each of R^{23}, R^{24}, and R^{25} is, independently, H, C_1-C_6 alkyl, halogen, or trifluoromethyl, each of R^{26}, R^{27}, R^{28}, and R^{29} is, independently, H or C_1-C_6 alkyl, and R^{30} is H, halogen, trifluoromethyl, OCF_3, NO_2, C_1-C_6 alkyl, C_1-C_8 cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 alkoxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, amino C_1-C_6 alkyl, or C_6-C_{18} aryl,

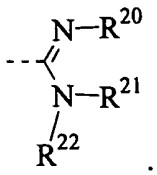
each of R^{12} and R^{13} is, independently, H, Cl, Br, OH, OCH_3, OCF_3, NO_2, and NH_2, or R^{12} and R^{13} together form a single bond.

Other analogs include stilbamidine (G-1) and hydroxystilbamidine (G-2), and their indole analogs (e.g., G-3).

5



Each amidine moiety in G-1, G-2, or G-3 may be replaced with one of the moieties depicted in formula (I) above as



As is the case for pentamidine, salts of stilbamidine and its related compounds are also useful in the method of the invention. Preferred salts include, for example, dihydrochloride and methanesulfonate salts.

Still other analogs are those that fall within a formula provided in any of U.S. Patent Nos. 5,428,051; 5,521,189; 5,602,172; 5,643,935; 5,723,495; 5,843,980; 6,008,247; 6,025,398; 6,172,104; 6,214,883; and 6,326,395, or U.S. Patent Application Publication Nos. US 2001/0044468 A1 and US 2002/0019437 A1, each of which is in its entirety incorporated by reference.

Exemplary analogs are 1,3-bis(4-amidino-2-methoxyphenoxy)propane, phenamidine, amicarbalide, 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,3-bis(4'-(N-hydroxyamidino)phenoxy)propane, 1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane, 1,5-bis(4'-(N-hydroxyamidino)phenoxy)pentane, 1,4-bis(4'-(N-hydroxyamidino)phenoxy)butane, 1,3-bis(4'-(4-hydroxyamidino)phenoxy)propane, 1,3-bis(2'-methoxy-4'-(N-hydroxyamidino)phenoxy)propane, 2,5-bis[4-amidinophenyl]furan, 2,5-bis[4-amidinophenyl]furan-bis-amidoxime, 2,5-bis[4-amidinophenyl]furan-bis-O-methylamidoxime, 2,5-bis[4-amidinophenyl]furan-bis-O-ethylamidoxime, 2,5-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,5-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,4-bis(4-amidinophenyl)furan, 2,4-bis(4-amidinophenyl)furan-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)furan-bis-O-4-fluorophenyl, 2,4-bis(4-amidinophenyl)furan-bis-O-4-methoxyphenyl, 2,5-bis(4-amidinophenyl) thiophene, 2,5-bis(4-amidinophenyl) thiophene-bis-O-methylamidoxime, 2,4-bis(4-amidinophenyl)thiophene, 2,4-bis(4-

amidinophenyl)thiophene-bis-O-methylamidoxime, 2,8-diamidinodibenzothiophene, 2,8-bis(N-isopropylamidino)carbazole, 2,8-bis(N-hydroxyamidino)carbazole, 2,8-bis(2-imidazolinyl)dibenzothiophene, 2,8-bis(2-imidazolinyl)-5,5-dioxodibenzothiophene, 3,7-diamidinodibenzothiophene, 3,7-bis(N-isopropylamidino)dibenzothiophene, 3,7-bis(N-hydroxyamidino)dibenzothiophene, 3,7-diaminodibenzothiophene, 3,7-dibromodibenzothiophene, 3,7-dicyanodibenzothiophene, 2,8-diamidinodibenzofuran, 2,8-di(2-imidazolinyl)dibenzofuran, 2,8-di(N-isopropylamidino)dibenzofuran, 2,8-di(N-hydroxylamidino)dibenzofuran, 3,7-di(2-imidazolinyl)dibenzofuran, 3,7-di(isopropylamidino)dibenzofuran, 3,7-di(N-hydroxylamidino)dibenzofuran, 2,8-dicyanodibenzofuran, 4,4'-dibromo-2,2'-dinitrobiphenyl, 2-methoxy-2'-nitro-4,4'-dibromobiphenyl, 2-methoxy-2'-amino-4,4'-dibromobiphenyl, 3,7-dibromodibenzofuran, 3,7-dicyanodibenzofuran, 2,5-bis(5-amidino-2-benzimidazolyl)pyrrole, 2,5-bis[5-(2-imidazolinyl)-2-benzimidazolyl]pyrrole, 2,6-bis[5-(2-imidazolinyl)-2-benzimidazolyl]pyridine, 1-methyl-2,5-bis(5-amidino-2-benzimidazolyl)pyrrole, 1-methyl-2,5-bis[5-(2-imidazolyl)-2-benzimidazolyl]pyrrole, 1-methyl-2,5-bis[5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-benzimidazolyl]pyrrole, 2,6-bis(5-amidino-2-benzimidazoyl)pyridine, 2,6-bis[5-(1,4,5,6-tetrahydro-2-pyrimidinyl)-2-benzimidazolyl]pyridine, 2,5-bis(5-amidino-2-benzimidazolyl)furan, 2,5-bis-[5-(2-imidazolinyl)-2-benzimidazolyl]furan, 2,5-bis-(5-N-isopropylamidino-2-benzimidazolyl)furan, 2,5-bis-(4-guanylphenyl)furan, 2,5-bis(4-guanylphenyl)-3,4-dimethylfuran, 2,5-bis{p-[2-(3,4,5,6-tetrahydropyrimidyl)phenyl]}furan, 2,5-bis[4-(2-imidazolinyl)phenyl]furan, 2,5[bis-{4-(2-tetrahydropyrimidinyl)}phenyl]-3-(p-tolyloxy)furan, 2,5[bis{4-(2-imidazolinyl)}phenyl]-3-(p-tolyloxy)furan, 2,5-bis{4-[5-(N-2-aminoethylamido)benzimidazol-2-yl]phenyl}furan, 2,5-bis[4-(3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)phenyl]furan, 2,5-bis[4-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-yl)phenyl]furan, 2,5-bis(4-N,N-dimethylcarboxhydrazidephenyl)furan, 2,5-bis{4-[2-(N-2-

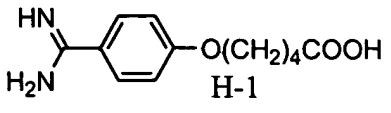
hydroxyethyl)imidazolinyl]phenyl}furan, 2,5-bis[4-(N-isopropylamidino)phenyl]furan, 2,5-bis{4-[3-(dimethylaminopropyl)amidino]phenyl}furan, 2,5-bis{4-[N-(3-aminopropyl)amidino]phenyl}furan, 2,5-bis[2-(imidzaolinyl)phenyl]-3,4-bis(methoxymethyl)furan, 2,5-bis[4-N-(dimethylaminoethyl)guanyl]phenylfuran, 2,5-bis{4-[(N-2-hydroxyethyl)guanyl]phenyl}furan, 2,5-bis[4-N-(cyclopropylguanyl)phenyl]furan, 2,5-bis[4-(N,N-diethylaminopropyl)guanyl]phenylfuran, 2,5-bis{4-[2-(N-ethylimidazolinyl)]phenyl}furan, 2,5-bis{4-[N-(3-pentylguanyl)]}phenylfuran, 2,5-bis[4-(2-imidazolinyl)phenyl]-3-methoxyfuran, 2,5-bis[4-(N-isopropylamidino)phenyl]-3-methylfuran, bis[5-amidino-2-benzimidazolyl]methane, bis[5-(2-imidazolyl)-2-benzimidazolyl]methane, 1,2-bis[5-amidino-2-benzimidazolyl]ethane, 1,2-bis[5-(2-imidazolyl)-2-benzimidazolyl]ethane, 1,3-bis[5-amidino-2-benzimidazolyl]propane, 1,3-bis[5-(2-imidazolyl)-2-benzimidazolyl]propane, 1,4-bis[5-amidino-2-benzimidazolyl]propane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]butane, 1,8-bis[5-amidino-2-benzimidazolyl]octane, trans-1,2-bis[5-amidino-2-benzimidazolyl]ethene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-methylbutane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-ethylbutane, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1-methyl-1-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-1,3-butadiene, 1,4-bis[5-(2-imidazolyl)-2-benzimidazolyl]-2-methyl-1,3-butadiene, bis[5-(2-pyrimidyl)-2-benzimidazolyl]methane, 1,2-bis[5-(2-pyrimidyl)-2-benzimidazolyl]ethane, 1,3-bis[5-amidino-2-benzimidazolyl]propane, 1,3-bis[5-(2-pyrimidyl)-2-benzimidazolyl]propane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]butane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-

methylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-ethylbutane, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1-methyl-1-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2,3-diethyl-2-butene, 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-1,3-butadiene, and 1,4-bis[5-(2-pyrimidyl)-2-benzimidazolyl]-2-methyl-1,3-butadiene, 2,4-bis(4-guanylphenyl)pyrimidine, 2,4-bis(4-imidazolin-2-yl)pyrimidine, 2,4-bis[(tetrahydropyrimidinyl-2-yl)phenyl]pyrimidine, 2-(4-[N-i-propylguanyl]phenyl)-4-(2-methoxy-4-[N-i-propylguanyl]phenyl)pyrimidine, 4-(N-cyclopentylamidino)-1,2-phenylene diamine, 2,5-bis-[2-(5-amidino)benzimidazoyl]furan, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]furan, 2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]furan, 2,5-bis[2-(5-amidino)benzimidazoyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]pyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]pyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]pyrrole, 1-methyl-2,5-bis[2-(5-amidino)benzimidazoyl]pyrrole, 2,5-bis[2-{5-(2-imidazolino)}benzimidazoyl]-1-methylpyrrole, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]-1-methylpyrrole, 2,5-bis[2-(5-N-isopropylamidino)benzimidazoyl]thiophene, 2,6-bis[2-{5-(2-imidazolino)}benzimidazoyl]pyridine, 2,6-bis[2-(5-amidino)benzimidazoyl]pyridine, 4,4'-bis[2-(5-N-isopropylamidino)benzimidazoyl]-1,2-diphenylethane, 4,4'-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]-2,5-diphenylfuran, 2,5-bis[2-(5-amidino)benzimidazoyl]benzo[b]furan, 2,5-bis[2-(5-N-cyclopentylamidino)benzimidazoyl]benzo[b]furan, 2,7-bis[2-(5-N-isopropylamidino)benzimidazoyl]fluorene, 2,5-bis[4-(3-(N-morpholinopropyl)carbamoyl)phenyl]furan, 2,5-bis[4-(2-N,N-dimethylaminoethylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N,N-dimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N-methyl-3-N-phenylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[4-(3-N, N^8,N^{11}-

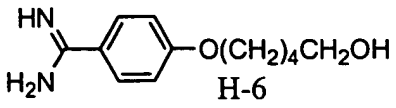
trimethylaminopropylcarbamoyl)phenyl]furan, 2,5-bis[3-amidinophenyl]furan, 2,5-bis[3-(N-isopropylamidino)amidinophenyl]furan, 2,5-bis[3[(N-(2-dimethylaminoethyl)amidino]phenylfuran, 2,5-bis[4-(N-2,2,2-trichloroethoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-thioethylcarbonyl) amidinophenyl]furan, 2,5-bis[4-(N-benzyloxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-fluoro)-phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4-(N-(4-methoxy)phenoxycarbonyl)amidinophenyl]furan, 2,5-bis[4(1-acetoxyethoxycarbonyl)amidinophenyl]furan, and 2,5-bis[4-(N-(3-fluoro)phenoxycarbonyl)amidinophenyl]furan. Methods for making any of the foregoing compounds are described in U.S. Patent Nos. 5,428,051; 5,521,189; 5,602,172; 5,643,935; 5,723,495; 5,843,980; 6,008,247; 6,025,398; 6,172,104; 6,214,883; and 6,326,395, an U.S. Patent Application Publication Nos. US 2001/0044468 A1 and US 2002/0019437 A1.

Pentamidine Metabolites

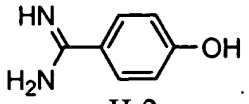
Pentamidine metabolites are also useful in the antiproliferative combination of the invention. Pentamidine is rapidly metabolized in the body to at least seven primary metabolites. Some of these metabolites share one or more activities with pentamidine. It is likely that some pentamidine metabolites will have anti-cancer activity when administered in combination with an antiproliferative agent. Seven pentamidine metabolites (H-1 through H-7) are shown below.



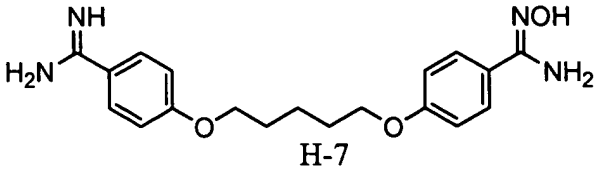
H-1



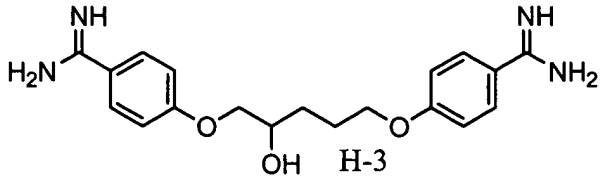
H-6



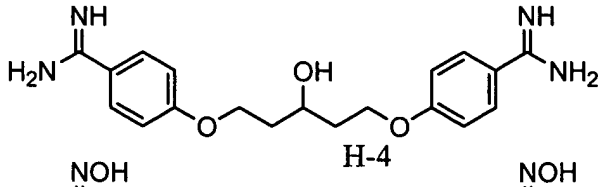
H-2



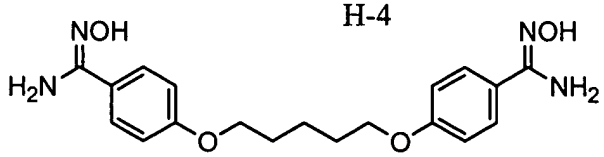
H-7



H-3



H-4



H-5

Therapy

The compounds of the invention are useful for the treatment of neoplasms. Therapy may be performed alone or in conjunction with another therapy (e.g., surgery, radiation therapy, chemotherapy, immunotherapy, anti-angiogenesis therapy, or gene therapy). For example, useful chemotherapeutic agents that can be used in conjunction with pentamidine or a pentamidine analog and chlorpromazine or a chlorpromazine analog are listed in Table (I) and are referred to a "Group A antiproliferative agents."

The duration of the combination therapy depends on the type of disease or disorder being treated, the age and condition of the patient, the stage and type of the patient's disease, and how the patient responds to the treatment. Therapy may be given in on-and-off cycles that include rest periods so that the patient's body has a chance to recovery from any as yet unforeseen side-effects.

Examples of cancers and other neoplasms include, without limitation, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (Hodgkin's disease, non-Hodgkin's disease), Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodenriglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

Formulation of Pharmaceutical Compositions

The administration of each compound of the combination may be by any suitable means that results in a concentration of the compound that, combined with the other component, is anti-neoplastic upon reaching the target region. The compound may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total

weight of the composition. The composition may be provided in a dosage form that is suitable for the oral, parenteral (e.g., intravenously, intramuscularly), rectal, cutaneous, nasal, vaginal, inhalant, skin (patch), or ocular administration route. Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: *The Science and Practice of Pharmacy*, 20th edition, 2000, ed. A.R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Dosages

The dosage of each compound of the claimed combinations depends on several factors, including: the administration method, the neoplasm to be treated, the severity of the neoplasm, whether the neoplasm is to be treated or prevented, and the age, weight, and health of the patient to be treated.

For combinations that include an anti-proliferative agent in addition to a chlorpromazine/chlorpromazine analog and pentamidine/pentamidine analog combination, the recommended dosage for the anti-proliferative agent is desirably less than or equal to the recommended dose as given in the *Physician's Desk Reference*, 57th Edition (2003).

As described above, the compound in question may be administered orally in the form of tablets, capsules, elixirs or syrups, or rectally in the form of suppositories. Parenteral administration of a compound is suitably performed, for example, in the form of saline solutions or with the compound incorporated into liposomes. In cases where the compound in itself is not sufficiently soluble to be dissolved, a solubilizer such as ethanol can be applied. Below, for illustrative

purposes, the dosages for chlorpromazine and pentamidine are described. One in the art will recognize that if a second compound is substituted for either chlorpromazine or pentamidine, the correct dosage can be determined by examining the efficacy of the compound in cell proliferation assays, as well as its toxicity in humans.

A chemotherapeutic agent of the invention is usually given by the same route of administration that is known to be effective for delivering it as a monotherapy. For example, when used in combination therapy with pentamidine or a pentamidine analog and chlorpromazine or a chlorpromazine analog according to the methods of this invention, a Group A antiproliferative agent is dosed in amounts and frequencies equivalent to or less than those that result in its effective monotherapeutic use.

Oral Administration

For chlorpromazine or a chlorpromazine analog adapted for oral administration for systemic use, the dosage is normally about 0.1 mg to 1000 mg per dose administered (preferably about 0.5 mg to 500 mg, and more preferably about 1 mg to 300 mg) one to ten times daily (preferably one to 5 times daily) for one day to one year, and may even be for the life of the patient; because the combinations of the invention function primarily as cytostatic rather than cytotoxic agents, and exhibit low toxicity, chronic, long-term administration will be indicated in many cases. Dosages up to 2 g per day may be necessary.

For pentamidine or a pentamidine analog, the dosage is normally about 0.1 mg to 300 mg per dose administered (preferably about 1 mg to 100 mg) one to four times daily for one day to one year, and, like chlorpromazine, may be administered for the life of the patient. Administration may also be given in cycles, such that there are periods during which time pentamidine is not administered. This period could be, for example, about a day, a week, a month, or a year or more.

Rectal Administration

For compositions adapted for rectal use for preventing disease, a somewhat higher amount of a compound is usually preferred. Thus a dosage of chlorpromazine or a chlorpromazine analog is normally about 5 mg to 2000 mg per dose (preferably about 10 mg to 1000 mg, more preferably about 25 mg to 500 mg) administered one to four times daily. Treatment lengths are as described for oral administration. The dosage of pentamidine or a pentamidine analog is as described for orally administered pentamidine.

Parenteral Administration

For intravenous or intramuscular administration of chlorpromazine or a chlorpromazine analog, a dose of about 0.05 mg/kg to about 5 mg/kg body weight per day is recommended, a dose of about 0.05 mg/kg to about 3 mg/kg is preferred, and a dose of 0.01 mg/kg to 2 mg/kg is most preferred. Pentamidine or a pentamidine analog is administered at a daily dose of about 0.05 mg/kg to about 20 mg/kg, preferably at a dose of about 0.05 mg/kg to about 10 mg/kg, and more preferably at a dose of about 0.1 mg/kg to about 4 mg/kg.

Each compound is usually administered daily for up to about 6 to 12 months or more. It may be desirable to administer a compound over a one to three hour period; this period may be extended to last 24 hours or more. As is described for oral administration, there may be periods of about one day to one year or longer during which at least one of the drugs is not administered.

Inhalation

For inhalation, chlorpromazine or a chlorpromazine analog is administered at a dose of about 1 mg to 1000 mg daily, and preferably at a dose of about 2 mg to 500 mg daily. For pentamidine or a pentamidine analog, a dose of about 1 mg to 1000 mg, and preferably at a dose of 2 mg to 600 mg, is administered daily.

Percutaneous Administration

For topical administration of either compound or analogs thereof, a dose of about 1 mg to about 5 g administered one to ten times daily for one week to 12 months is usually preferable.

The following examples are to illustrate the invention. They are not meant to limit the invention in any way.

Examples

Chemicals and Drug Preparation

5-flurouracil (5-FU), paclitaxel, chlorpromazine and pentamidine were all purchased from Sigma Chemical Co. (St. Louis, MO). Chlorpromazine and pentamidine were prepared in phosphate buffered saline (PBS) containing 10% (v/v) EtOH. 5-fluorouracil was initially dissolved in ethanol and diluted in distilled water to a final concentration of 5% (v/v) ethanol. A stock solution of paclitaxel was prepared using a 1:1 (v/v) emulsion of Cremophor EL/ethanol. The paclitaxel stock was diluted 1:6 (v/v) with 0.9M NaCl immediately prior to injection. A combination of chlorpromazine and pentamidine, henceforth referred to as "C/P combination", was administered as two separate injections..

Human Tumor Cells.

The human lung adenocarcinoma tumor cell line, A-549, and human colon cancer cell line, HCT 116, were purchased from American Type Culture Collection (Rockville, MD). A549 cells were grown in DMEM and HCT 116 cells were grown in McCoy's 5A media, each supplemented with 10% fetal bovine serum (FBS), at 37°C in a humidified incubator containing 5% CO_2. Cell cultures were approximately 80% confluent at time of harvest.

Xenograft Models.

All experiments were carried out using male or female 6-8 week old SCID Hsd:ICR(CD-1) mice (Harlan, Indianapolis, IN). A-549 cells were harvested, resuspended in DMEM minus serum, and injected subcutaneously into the right flanks (4×10^6 cells/flank in a 300 μL volume). HCT 116 cells were harvested, resuspended in McCoy's 5A minus serum, and injected subcutaneously into the right and left flanks ($5 \times 1\ 0^6$ cells/flank in a 300 μL volume). Tumor volumes were determined by measuring the length (l) and the width (w) and calculating the volume ($V = lw^2/2$). Depending on the study, the tumors were between about 150 mm^3 – about 800 mm^3 at the time of animal randomization into treatment groups (n = 8-10 mice per group).

Unless otherwise stated, drugs were administered daily Monday to Friday. Paclitaxel was administered 3 days per week, Monday, Wednesday, and Friday only. All drugs were administered by intraperitoneal injection in a volume of 100 μL/25 grams. Animals undergoing combination therapy received two individual injections for a total of 200 μL per mouse. Control animals received 200 μL injections of vehicle only.

Treatment of mice with C/P combination was generally well tolerated, with no severe adverse events noted. The major side effect observed was sedation, which occurred within 10 minutes of C/P combination or chlorpromazine administration. The sedation was found to last up to 24 hrs in the highest C/P combination doses utilized (10 mg/Kg chlorpromazine, 20 mg/Kg pentamidine). The prolonged sedation seen in the higher doses of C/P combination was accompanied by hypothermia and some bodyweight loss in these animals. Lower doses of either C/P combination or chlorpromazine resulted in a reduced period of sedation and associated hypothermia, increasing animal survival.

Statistical Analysis.

Evaluation of the results included statistical analysis of differences in tumor size between test and control groups at the end of each treatment period. Group means were compared using a one-way ANOVA. If the ANOVA was significant, i.e., $p \leq 0.05$, a Dunnett's multiple comparison test was used to determine which groups were different. Only animals surviving to the completion of the treatment period were included in the analysis.

Example 1. Dose optimization of chlorpromazine/pentamidine in human lung tumor xenografts.

Combinations of 10 mg/Kg chlorpromazine and 20 mg/Kg pentamidine or 7.5 mg/Kg chlorpromazine and 20 mg/Kg pentamidine were investigated in a human lung tumor xenograft model. A549 cells were injected subcutaneously into female SCID mice and the tumor volumes were allowed to reach about 400 mm^3 prior to animal randomization. Animals were administered one of the above combinations or saline vehicle control intraperitoneally five times per week (each day, Monday through Friday) for two weeks

The administration of both 10 mg/Kg chlorpromazine and 7.5 mg/Kg chlorpromazine combinations resulted in substantial reductions of tumor volumes, 56% and 48%, respectively when compared with control. The tumor volume reductions for these combinations were consistently smaller than that observed for the animals treated with high dose, high frequency paclitaxel at a dose of 20 mg/Kg (See Table I). Although tumor growth inhibition was observed with these two combinations, sedation and hypothermia were also evident.

Using the same protocol as that described above, a combination of 5 mg/Kg chlorpromazine and 20 mg/Kg pentamidine limited the sedation side effects while maintaining anti-tumor activities. In this study, tumor volume was still reduced to 42% of that observed in the vehicle control animals (FIG. 1). Animals treated with paclitaxel (20 mg/Kg) had tumors that were 24% smaller than those observed

in vehicle controls and mice receiving chlorpromazine or pentamidine alone exhibited no decrease in tumor volumes compared to control animals.

Example 2. Effect of dosing regimen on chlorpromazine/pentamidine activity in human lung tumor xenografts.

A multiweek treatment regimen of a combination of 5 mg/Kg chlorpromazine and 20 mg/Kg pentamidine was investigated in a human lung tumor xenograft model. A549 cells were injected subcutaneously into male SCID mice and the tumor volumes were allowed to reach about 400 mm^3 prior to animal randomization. Animals were administered drug combination or vehicle control intraperitoneally five times per week (each day, Monday through Friday) for three weeks. Treatment was stopped for a one week recovery period, then continued as before for an additional two weeks. Results for this multi-week treatment regimen are shown in FIG. **2**.

During the first treatment period, tumor volumes in the chlorpromazine/pentamidine treated animals were consistently smaller then the vehicle control and single agent treated animals. At the end of the first treatment phase, treated tumors were 29% smaller than the control group. After cessation of the first treatment phase, tumors in the treatment group grew at a 37 % slower rate compared to the vehicle control during the one week recovery period. On recommencing treatment, only tumor growth in the treatment group was inhibited. At the conclusion of the second treatment period it was observed that, over the course of the entire treatment period, tumor volumes for the chlorpromazine/pentamidine-treated group were reduced by 50% when compared to the vehicle treated animals.

Paclitaxel (20 mg/Kg) treated animals (not shown in FIG. **2**) had tumor volumes that were 27% less than the vehicle control animals at the of the first treatment period, but then had to be sacrificed as a result of cumulative drug toxicity.

Table I: Summary of C/P Combination Dose Ranging Studies

Combination Dosage	Tumor Cell Line	Dose Regimen - Combination	Reduction in Tumor Volume (% decrease relative to control)	
			C/P Combination	Positive Control
10 mg/Kg Chlorpromazine 20 mg/Kg Pentamidine	A549	5 days/week (M-F) 2 week treatment	56 %	29 % Taxol 20 mg/Kg (M,W,F)
7.5 mg/Kg Chlorpromazine 20 mg/Kg Pentamidine	A549	5 days/week (M-F) 2 week treatment	48 %	24 % Taxol 20 mg/Kg (M,W,F)
5 mg/Kg Chlorpromazine 20 mg/Kg Pentamidine	A549	5 days/week(M-F) 2 week treatment	42 %	24 % Taxol 20 mg/Kg (M,W,F)
5 mg/Kg Chlorpromazine 20 mg/Kg Pentamidine	A549	5 days/week (M-F) 3 week treatment 1 week off treatment 2 week treatment	[a] 29 % [b] 50 %	N/A Taxol 20 mg/Kg (M,W,F)
5 mg/Kg Chlorpromazine 20 mg/Kg Pentamidine	HCT 116	5 days/week (M-F) 2 week treatment	59 %	47 % 5-FU 25 mg/Kg (M-F)
5 mg/Kg Chlorpromazine 10 mg/Kg Pentamidine	HCT 116	5 days/week (M-F) 2 week treatment	44 %	N/A
5 mg/Kg Chlorpromazine 10 mg/Kg Pentamidine	HCT 116	3 days/week (M, W, F) 2 week treatment	37 %	N/A
2.5 mg/Kg Chlorpromazine 10 mg/Kg Pentamidine	HCT 116	3 days/week (M, W, F) 2 week treatment	32 %	N/A

[a]End of first treatment phase
[b]End of second treatment phase

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is: